UNIVERSITY OF MALAYA

INSPIRATION AND PERSPIRATION : THE ACADEMIC JOURNEY OF A PAEDIATRIC ONCOLOGIST

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Department of Paediatrics
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Inaugural Lecture

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Biography

Professor Dr. Hany Ariffin

MBBS (Malaya), MPaed (Malaya), PhD (Malaya) MRCP(UK) , FRCPCH

Professor Hany Ariffin was born in Petaling Jaya. After completing her secondary education in Tunku Kurshiah College, she along with a band of socialist-minded school-mates, enrolled in Pusat Asasi Sains, Universiti Malaya (UM) with the intention of pursuing a medical career.

Professor Hany received her MBBS degree from UM in 1992. Originally, she was posted to Hospital Alor Setar for her housemanship. However, intervention from Professor Lin Hai Peng, Head of Paediatrics (1991-2000) led to her secondment from the Ministry of Health to the Ministry of Education. This marked the start of her 20-year affiliation with UM and the University Hospital (as UMMC was known then). After completing her internship in University Hospital, she trained in paediatrics and subsequently sub-specialised in paediatric haematology-oncology under the mentorship of Professor Lin . She officially joined as an UM academic staff in 1997 after obtaining her MRCP(UK) qualifications and was conferred her Master of Paediatrics degree the following year. Her service to UM was only interrupted during training stints at Great Ormond Street Hospital in London, the Royal Victoria Infirmary in Newcastle and National University Hospital in Singapore.

Currently, Professor Hany is professor of paediatrics and consultant paediatric oncologist at the University of Malaya Medical Centre (UMMC). She was appointed as Head of the University of Malaya Cancer Research Institute (UMCRI) in 2009. Under her leadership, UMCRI has grown to accommodate different cancer research groups under its umbrella. The expansion of cancer research naturally led to the birth of a cancer biorepository facility, also known as the Biobank Unit, in the Faculty of Medicine which she also heads.

Prof Hany's main research interest is in childhood leukaemia and she has been the Malaysian lead investigator for the Malaysia-Singapore (MASPORE) Leukaemia Study Group since 2003. Her other research interests include blood disorders in children with Down Syndrome and inherited cancers, particularly related to mutations in the tumour suppressor gene, *TP53*. Her team focuses on epidemiology of the Li- Fraumeni cancer predisposition syndrome in Malaysia as well as understanding the molecular genetics that determine the phenotypic heterogeneity of this condition.

Professor Hany is the immediate past-president of the Malaysian Society of Paediatric Haematology-Oncology. She is a Fellow of the International Union Against Cancer as well as a member of the International Society of Paediatric Oncology. She also sits in the paediatric haematology-oncology credentialing sub-committee of the National Specialist Register. Most of her spare time is spent on fund-raising activities for her children's cancer charities but she wishes she had more time to indulge in her new favourite pastime - gardening.

SYNOPSIS

Opportunities and challenges are part and parcel of academia. Challenges are often aplenty; however, if grasped and handled astutely can be turned into lessons for self-education and improvement. Similarly, opportunities occur around us in subtle abundance and should be seized whenever possible. Ideas and inspiration can be realised when challenges are overcome by innovation and hard work. The ability to overcome barriers and embrace opportunities is essential especially when juggling the desire to improve clinical service in tandem with personal development and realising aspirations of an academic institution. In this lecture, the speaker will allude to events in her clinical practice which have spawned ideas for research. She will also share experiences of meeting inspirational individuals who have helped shape her training in paediatric oncology as well as influence research direction.

Paediatric Oncology : Overview

Cancer is predominantly a disease of ageing and is rare in childhood. The incidence of cancer in a child aged 15 years or less is approximately 1 in 6500 compared to 1 in 200 in adults (Ries, 2008). In 2005, the United States SEER Database reported an incidence of 159 cases of cancer per million population in children aged 0-14 years. The Malaysian National Cancer Registry reported that the incidence of cancer in Peninsular Malaysia was 75.5 per million children and adolescents aged between 0 to 19 years with approximately 1600 new cases diagnosed each year (Lim, 2002).

In America and the West, the journey of paediatric oncology has been one of great achievements. In the 1940's, the stated average age of survival after diagnosis of acute lymphoblastic leukaemia (ALL) was less than 3 months. Two decades later, in a global survey of haematologists in 1965, Drs Joseph Burchenal and Lois Murphy were able to identify only 71 children in the entire world with ALL who had survived more than 5 years (Burchenal, 1965).

The modern era of leukaemia therapy began when Dr Sidney Farber of Boston's Children Hospital was able to induce remission in children with ALL using the folate antagonist, aminopterin in 1948. Following Dr Farber's report, new anti-leukemic drugs were introduced. These included 6-MP in 1953, L-asparaginase in 1961, vincristine in 1962 and thereafter, corticosteroids and nitrogen mustard. Notably, many of these drugs are used to this day. Modern therapeutic protocols now use, in a protracted continuous manner, a combination of cytotoxic agents that work synergistically resulting in a cure rate of over 80% in many countries. Better understanding of lymphoblast biology via immunologic and cytogenetic techniques have allowed the implementation of stratified therapies to attain the best survival rates with least morbidity possible (Pui, 1998).

The phenomenal success in the treatment of childhood leukaemia has also been mirrored in many other paediatric cancers. The use of combination chemotherapy in tandem with advances in surgery and radiotherapy have significantly improved outcome of childhood solid tumours which hitherto were inevitably lethal. However, what has underlined these

great strides in paediatric oncology has been the establishment of large, multi-institutional cooperative therapy groups. These research groups were able to enrol relatively large numbers of patients and hence were able to assess the effectiveness of various therapeutic protocols and associated treatment-related toxicities. Today, in addition to national groups e.g. Children's Oncology Group of USA and the UK Children's Cancer Study Group, paediatric oncologists world-wide participate in global trials under the auspices of the International Society of Paediatric Oncology (SIOP) allowing rapid assessment of evidence-based therapies even for rare malignancies.

Paediatric Oncology in Malaysia : Perspective from University of Malaya

The Department of Paediatrics was established in the Faculty of Medicine, University of Malaya in 1966. However, provision of clinical services only commenced after the University Hospital was established in 1968. In the salad days of paediatric oncology in Malaysia, children with cancer were treated by general paediatricians and treatment regimens were based on opinions of individual consultants. The first two paediatricians who focused on managing children with cancer were Professor Devandralingam Sinniah and Professor Lin Hai Peng. In 1978, Professor Sinniah reported in the journal *Cancer* that 4 out of 10 patients in UMMC who had good prognostic features survived 3 years following diagnosis (Sinniah, 1978). These results would be considered criminal by today's standards !

Professor Lin was a man of vision and great tenacity. He built a team of committed paediatric oncologists as well as actively recruited young doctors. In 1987, Professor Lin pioneered bone marrow transplantation in Malaysia and today, more than 350 haematopoeitic stem cell transplants have been performed in UMMC from both sibling and matched unrelated donors. Professor Lin was assisted by two able lieutenants who were outstanding paediatric oncologists in their own right: Professor Wan Ariffin Abdullah and Professor Chan Lee Lee. Both of them served UMMC until retirement allowing stability and continuity in the unit.

The second generation of 'young turks' were Drs Shekhar Krishnan, Chong Lee Ai and yours truly (although none of them are quite so young

now). Like well-fitting cogs in a machine, the team members brought their individual set of skills to the group whilst being able to complement each other. There was a conscious effort to improve quality in all aspects of patient care including standardising treatment protocols, developing supportive care guidelines and auditing patient outcomes.

In recent years, more youthful vigour has been injected into the team in the form of Drs Revathi Rajagopal, Lum Su Han and Yap Tsiao Yi. On their shoulders they carry the legacy built in the 1970's of continuously striving to improve the UMMC children's cancer unit to reach international standards.

Inspiration and Perspiration : My Journey

First impressions of life as a paediatric oncologist was gleaned when I was a medical student. Of all the paediatric sub-specialities, the doctors working in oncology constantly appeared busy and buzzing on the ward. "Exciting" events like resuscitation of collapsed patients and invasive procedures were common; these often are a source of morbid fascination to students. The lecturers would pop into the ward several times in a day and we actively participated in ward work, accompanying patients to scans and assisting the harried house-officers. Soon after the final MBBS examinations, Professor Lin Hai Peng the then Head of Paediatrics met students that had been identified as 'having academic potential'. I was invited to a one-to-one interview with him and his words of encouragement left a significant mark on me - as it would have on any impressionable medical student. It has to be said that encouragement from teachers at an early stage of a young doctor's life is sometimes enough to influence a career choice – akin to the effect of a particular cytokine in determining the maturing pathway of a previously uncommitted stem cell.

The early years of training, as any post-graduate trainee would attest to, were tough. Clinical and on-call duties were physically challenging. The old paediatrics block was devoid of air-conditioning. At night all the windows were shut, which meant that on-call duties had to be performed in an environment of unbearable heat. Coupled with spartan facilities and an on-call allowance of RM1.25 per hour, this was very close to modern-day slavery. In addition, we had the pressures of passing examinations

and many of us sat for both the local Masters examinations as well as the British professional examinations. Nevertheless, these were halcyon days of discovery and camaraderie which I cherish.

My early involvement in research began with studying infectious complications in children undergoing chemotherapy. Epidemiology of bloodstream pathogens was easy enough to study and had a tangible importance in patient management. It was too early to make any significant contribution to designing or modifying treatment protocols especially when understanding of cancer biology was still raw. Some of the early publications related to infections and febrile neutropenia were :

1] Ariffin H , Parasakthi N, Mahfuzah M , Arasu A , Ariffin WA , Chan LL , Lin HP . Ceftazidime-resistant *Klebsiella pneumoniae* bloodstream infection in children with febrile neutropenia. *Int J Infect Dis* 1999; 4 : 21 - 25

2] Ariffin H , Arasu A, Mahfuzah M, et al. Single-daily ceftriaxone plus amikacin vs thrice-daily ceftazidime plus amikacin as empirical treatment of febrile neutropenia in children with cancer. *J Paed Child Health* 2001; 37(1) :38 - 43

3] Parasakthi N and Ariffin H (eds) . Consensus Guidelines on the management of infections by ESBL- producing bacteria. 2001; Joint publication by the Ministry of Health , Malaysia , Academy of Medicine Malaysia and Malaysian Society of Infectious Diseases and Chemotherapy (MSIDC)

In 2002, after approximately 5 years of service in the paediatric oncology unit, I was allowed to pursue training stints overseas. Research-wise, I had only been concentrating on infections in the immunocompromised host. Now, I wanted to address the very reason these children were immunocompromised in the first place : they had cancer. However, making any impact at all in patient survival rates eg by modifying chemotherapy protocols seemed a formidable task. I was a mere clinician with no basic science or molecular biology training and had no idea where to start.

Also in 2002 , Ipoh-born Dr Allen Yeoh returned to the National University of Singapore (NUS) after completing a 3-year fellowship at the world-renowned St Jude Children's Research Hospital in Memphis. He was a bright, young star in NUS and had recently won the Singapore Youth Award for Science and Technology. In addition, he had just published a paper on ALL genetic subtypes which made the cover of *Cancer Cell* (Yeoh, 2002).

Later that year, Dr Allen Yeoh and his team travelled 500km north to Kuala Lumpur to start discussions with Professor Lin for the development of a new common protocol for treating children with ALL. At that time, UMMC had just completed a trial, the UH-ALL95 protocol, which was modified from a recent Dutch protocol for childhood ALL. The philosophy of the UH-ALL95 protocol was to deliver a simple, yet effective treatment regimen for children who originated in states without a resident paediatric oncologist. Unlike Singapore, patients treated in UMMC resided in the various states of Peninsular and East Malaysia with portions of the protocol administered by general paediatricians and medical officers. From 1995 to 2002, the UH-ALL95 protocol accrued 339 patients. 6-year event-free survival (EFS) was only 56%; and even those in the lowest-risk category had an EFS rate of only 67% (Ng, 2000) – far from the Western rates of 75-80%. Clearly, there was a pressing need for a better treatment regimen.

The team from Singapore would provide the technical expertise and funding whilst the UMMC site had the patient numbers to allow meaningful research to be carried out. As part of my Hadiah Latihan Cuti Belajar scholarship, I had initially planned a 6-month training stint in Singapore to remain close to home. Little did I imagine that my decision to train in NUS (which were for selfish reasons) for would be the nidus for a long-standing collaborative partnership between Allen and I. Together, our two centres (now named "MASPORE Leukaemia Study Group") developed a synergy which later translated into overwhelming success.

My months in Singapore were an exercise in humility. As a complete novice in molecular laboratory techniques, I was required to learn processing of bone marrow samples as well as cell banking and PCR in addition to safe lab practices, inventory of samples, coding, etc in order to set up a 'satellite' lab in UMMC. This was crucial for the smooth

running of the MASPORE-ALL clinical trial. There was no formal instructor assigned to me and I had to rely on the patience and goodwill of the lab staff; some of whom were still sporting pubescent acne. That they endured frayed tempers and frazzled nerves to train a laboratory plebeian like me deserves gratitude and respect.

Two hitherto unavailable laboratory tests were incorporated into the study. Minimal residual disease monitoring using IgH, Ig*k* and T-cell receptor rearrangements were performed in the central lab in NUS whilst screening for oncogene fusion transcripts was performed in UMMC. These tests were vital for the accurate identification of risk-groups and appropriate allocation of treatment intensity. For example, patients who had poor prognostic transcripts namely *BCR-ABL1* were allocated to the high-risk arm which incorporated additional anthracyclines and bone marrow transplantation. Treatment response was monitored by measuring minimal residual disease levels. Patient data and laboratory results were updated by both centres in real-time via a dedicated secure website.

The need for these sophisticated lab tests served as the impetus to develop the paediatric oncology research laboratory. Many pieces of important equipment were purchased using donations from charitable organisations. In 2004, one of our unit's staunch supporters, Datuk Seri Michael Chong facilitated donation of our first thermal cycler from the Malaysian Chinese Association. Subsequently, funds were raised for the purchase of consumables and payment of staff salaries.

In 2010, the study was closed for analysis. Five hundred and fifty-six patients had been accrued of whom 60% originated from UMMC. It was with great pride that the MASPORE-ALL group announced the results of the trial. The overall 6-year EFS was 80.8% with standard-risk patients achieving an EFS of 92%. These excellent results were highlighted in the media on both sides of the Causeway, bringing great repute to UM. The study and its outcomes were published in *Journal of Clinical Oncology* (Yeoh, 2012) further cementing a successful collaboration between two institutions whose histories date back to more than 100 years.

Currently, the MASPORE group is running the MASPORE-ALL2010 study which aims to replicate the success of the earlier trial but with

reduced treatment intensity, and consequently side-effects, in the low-risk category of patients.

In 2007, a family fulfilling the criteria for Li-Fraumeni Syndrome (LFS) was identified. The Li-Fraumeni Syndrome (LFS, OMIM 151623) and its variant form, Li-Fraumeni-like (LFL) are very heterogeneous forms of autosomal dominant cancer predisposition syndromes, which are characterized by clustering of early-onset cancers of the central nervous system, soft tissue sarcoma, osteosarcoma and premenopausal breast cancer. In addition, families matching these characteristics tend to have an increased risk of a wide spectrum of common cancers before the age of 50 years. Germline mutation in the tumour suppressor gene *TP53* is the only known genetic defect underlying LFS/LFL. Mutations are identified in 20% to 70% of families matching clinical definitions of LFL or LFS, respectively.

In the ethnic Malay kindred that we identified, the proband was a 7-year old girl who had been treated for rhabdomyosarcoma in infancy. Unfortunately, she suffered a relapse in the brain seven years on. Her sister had also been diagnosed in UMMC with adrenal carcinoma at the age of 6 months whilst her mother had developed bilateral breast cancer at 26 years of age. Genetic studies of this family led to the discovery of a novel mutation in their *TP53* gene (duplication of a 6-bp motif, GGCGTG in codon 334 of Exon 10) resulting in an in-frame insertion of two amino acid residues, repeating residues 334 (Gly) and 335 (Arg) (Ariffin, 2008). However, being novices in mutation analysis, we needed to identify an accredited laboratory where our findings could be verified.

Emails were sent to many international experts in the field to confirm the results and to gain input on the predicted outcome of this mutation on the p53 protein. Many remained without reply. However, response from Dr Pierre Hainaut, who at that time was Head of the Molecular Carcinogenesis Section at the International Agency for Research in Cancer (IARC/WHO) and a chance phone conversation then led to other collaborative projects and more importantly, friendship. Professor Pierre Hainaut has now visited Malaysia several times and most recently in July 2013 as a UM Academic Icon.

Paediatric Oncology in UMMC : Future Directions

The work of a paediatric oncologist is not done until all children can be successfully cured of cancer. However, such idealistic goals will remain unattainable. For the paediatric oncology unit in UMMC being in a country with limited resources, targets have also to be matched with available infrastructure and manpower.

One plan is to develop facilities for haematopoietic stem cell transplantation (HSCT) from a haploidentical donor, namely a parent. This will allow children to undergo allogeneic HSCT even if they did not possess a matched sibling donor, removing the exorbitant cost of procuring a HLA-matched cord blood unit from an overseas bank. This procedure requires expertise in manipulating donated stem cells to be used as a curative option whilst avoiding graft-versus-host disease. Graft-versus-host disease will result if cells from a donor who is not completely HLA-matched (and a haploidentical donor is only 50% matched with the recipient) are used. Thus, special techniques are needed to avert this potentially lethal complication.

The MASPORE group is also embarking on novel studies on leukaemia with centres in the Asia-Pacific region, namely Hong Kong and Japan. Trials involving patients in this region will complement studies conducted in predominantly Caucasian populations; e.g. by the American Children's Oncology Group and the German BFM (Berlin-Frankfurt-Munchen) consortium.

Another group of patients who will be studied in the next three years are long-term survivors of childhood ALL, namely the children who were treated using the MASPORE-ALL2003 protocol. Although usually effective in children, ALL therapy is toxic and has the potential to damage or interfere with function in many organ systems. It is well-known that children who survive ALL and its treatment have significantly elevated risks for second malignancies, myocardial infarction, obesity, metabolic disorders and neuro-cognitive deficit (Ness, 2011). These chronic conditions, alone or in combination, contribute to poor health outcomes. Thus, focused research on this cohort of patients will allow the concept of holistic therapy to be applied. The premise of "cure at all costs" for treating childhood cancer is no longer acceptable and treatment protocols are now designed recognizing these long-term implications.

In conclusion, today I am tall because I stand on the shoulders of giants. My academic journey has been one of inspiration and perspiration; I have been blessed by meeting inspirational and generous individuals – but there is still far to go. What would I hope my legacy to be? Far more important than the successful research programs and high patient cure rates, albeit important in their own right, would be the inculcation of the unit's ethos into the hearts and minds of the junior staff; where courage to affect change is never confused with arrogance; where temperament, but never principles, is practiced in moderation; and the rights of a child is always maintained supreme.

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Curriculum Vitae

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B) Career History

Jul 87 – Jul1992 : Undergraduate at the Medical Faculty, University of Malaya;
Graduated with MB,BS (Malaya) degrees in July 1992

Jun 98 – Mar 2002 : Lecturer, Paediatric Haematology-Oncology Unit, University of Malaya Medical Centre

Aug 00 – Oct 2000 : Fellow in paediatric haematology-oncology, Great Ormond Street Hospital, London, United Kingdom

Mar 02 – Aug 2002 : Clinical Fellow in paediatric oncology, Royal Victoria Infirmary,
Newcastle Upon Tyne Hospitals NHS Trust, United Kingdom

Sep 02 – Mar 2003 : Honorary Fellow in clinical and laboratory haematology , National University Hospital, Singapore

Jul 07 – Aug 2007 : Visiting Professorial Fellow; Queen Mary University of London (Cancer Research-UK Children's Cancer Group)

Dec 2009 – present : Professor and Senior Consultant Paediatric Oncologist, UMMC

C) Academic and Professional Qualifications:

1. 1992 - Bachelor of Medicine & Bachelor of Surgery, University of Malaya
2. 1997 - Membership of the Royal College of Physicians (UK)
3. 1998 - Masters of Paediatrics, University of Malaya
4. 2009 - Doctor of Philosophy, University of Malaya
5. 2012 - Fellow; Royal College of Paediatrics and Child Health (United Kingdom)

D) Professional Affiliations :

1. Fellow; International Union Against Cancer (UICC)
2. Member; International Society of Paediatric Oncology (SIOP)
3. Member; Malaysian Paediatric Association
4. Member; Malaysian Society of Paediatric Haematology -Oncology

E) Awards and Fellowships:

1998 - Postgraduate Merit Award; Malaysian Paediatric Association

2000 - Bill Marshall Memorial Fellowship; Great Ormond Street Hospital and Institute of Child Health, London

2000 - Young Investigator Travel Scholarship; International Society of Paediatric Oncology (SIOP)

2001 - Cancer Research Award; National Cancer Council of Malaysia (MAKNA)

2002 - UICC (International Union Against Cancer) Fellowship; Sir James Spence Institute of Child Health, Royal Victoria Infirmary, Newcastle-Upon-Tyne

2006 - UICC Fellowship; Cancer Research-UK Clinical Centre, London, United Kingdom

F) Publications

H-index : 12

Total citations : 503

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CV updated Aug 2013

Discussion on the ward corridor with A/Profs Shekhar Krishnan and Chong Lee Ai

Receiving award from the Chancellor for PhD candidate with highest cumulative ISI Impact Factor points in 2009

With staff of the pathology laboratory of St Bart's Hospital, London where most of the immunohistochemistry component of my PhD project was performed

Receiving a donation from PLUS Berhad for the Children's Cancer Unit

Birthday party on the paediatric oncology ward. Every opportunity to celebrate is seized

With fellow speakers Drs Pierre Hainaut and Maria-Isabel Achatz after attending a seminar on Li-Fraumeni Syndrome in Princeton, New Jersey. Visit to Albert Einstein's residence (he wasn't home)

Annual Children's Party – with fellow Manchester United supporters !

Group discussion in the paediatric oncology laboratory with our Academic Icon, Dr Pierre Hainaut

Every teacher's joy – with research assistants Siti Sarah Daud and Kamariah Ibrahim on their convocation day (both received M Biomed Sc degrees)

Parents and volunteers of CARES ; the support group for children's cancer units in Malaysia

Challenging senior managers of Bursa Malaysia to a game of foosball during a charity event. It is important to lose gracefully to people who want to donate money to your cause

With students and RA's of the Paediatric Oncology Research Group with our latest piece of laboratory equipment